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Neurobehavioral Profiles of Children With Neurofibromatosis 1 Referred for Learning Disabilities Are Sex-Specific

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We compared neurobehavioral profiles of 10 children with neurofibromatosis 1 (NF-1) referred for evaluation of learning disabilities (NF/LD) to those of learning disabled children without known genetic disease (LD), matched for age, sex, and estimated IQ. It was hypothesized that the NF/LD children would exhibit a neurobehavioral profile diagnostic of compromise of frontal/subcortical brain systems while those of the case controls would be heterogeneous.

Records from a clinic data base were reviewed retrospectively for the neurological and neuropsychological components of an interdisciplinary learning disabilities evaluation. Neurological abnormalities were more frequent in the NF/LD group, involving gross and fine motor coordination, praxis, and megencephaly. As predicted, clinical neuropsychological diagnostic ratings and composite neurobehavioral observation scores were consistent with compromise of frontal systems in the NF/LD group. An unanticipated finding was that outcomes in the NF/LD group were sex dependent: Megencephaly was observed in females only; and the frontal/subcortical neurobehavioral profile was more consistently observed in females. Females with NF-1 with megencephaly may be at increased risk for a neurobehavioral syndrome contributing to LD that is consistent with compromise of frontal/subcortical brain systems.

KEY WORDS: neurofibromatosis 1, genetic disease, neurological abnormalities

INTRODUCTION

Learning Disorders in Children With Neurofibromatosis 1 (NF-1)

NF-1 is a common autosomal dominant neurogenetic disorder with a prevalence of 1 in 4,000. Children with NF-1 have multiple cafe-au-lait spots on the skin and neurofibromas, and they are at risk for developing malignant tumors of the nerves throughout the neuroaxis. One of the most common complications is learning disability (LD), estimated to occur in 30–70% of children with NF-1 [NNF Conference Series, 1988; Huson, 1989; North et al., 1994].

Neuropathological and magnetic resonance imaging (MRI) studies of NF-1 have identified abnormalities in subcortical structures, specifically the globus pallidus and deep cerebral white matter [Rosman and Pearce, 1967; Duffner et al., 1988; Bawden et al., 1994; Hofman et al., 1994]. These abnormalities have not, however, been associated with focal neurological deficits [Duffner et al., 1989]. Such structural subcortical abnormalities may represent aberrations of neuronal migration or areas of demyelination and remyelination [Pont and Elster, 1992; Sevick et al., 1992].

Whether there is a specific behavioral phenotype associated with NF-1 remains unclear. When Eldridge et al. [1988] compared NF-1 children to unaffected sibs, they documented a higher incidence of minor signs of neurological impairment (motor abnormalities involving station, balance, and gait), lower IQ, and poorer performance on a task that measures judgment of line orientation. No excess of mental retardation, attention deficit hyperactivity disorder, or specific learning disorders was found. Other studies document nonverbal LDs most consistently [Bawden et al., 1994; Eliason, 1988; Varnhagen et al., 1988; Stine and Adams, 1989; Wadsby et al., 1989; Moore et al., 1994]. Although no personality differences were identified, the NF-1 children did elicit higher scores for aggressive/hyperactive behavior [Varnhagen et al., 1988]. Larger-scale studies described more global deficits in NF-1 children, consisting of both language-based and nonverbal LDs [North et al., 1994; Hofman et al., 1994]. When compared to sibs, children with NF-1 had significantly poorer performance in written language, reading, and

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neuromotor function [Hofman et al., 1994]. In a population study of NF clinic subjects, children were found to have a lower Full Scale IQ and diminished performance on language, visual motor integration, and coordination [North et al., 1994]. In both studies, low cognitive ability as measured by Full Scale IQ was correlated with the characteristic lesion found on MRI (T_2-weighted hyperintensity).

Such studies, however, have been conceptualized primarily in terms of strengths and weaknesses of specific cognitive skills as measured by psychometric testing. The aim of the present study was to specify neurobehavioral diagnostic profiles, which are conceptually referable to a neural substrate, for a series of children with NF-1 referred for evaluation of LD. These profiles extend beyond specific cognitive functions as measured by formal tests to include structured behavioral observation as well.

Specifically, we tested the hypothesis, suggested by the neuroimaging and neuropathological evidence, that children with NF-1 will show neurobehavioral profiles consistent with compromise of functions associated with anterior/subcortical brain systems. We predicted that neurobehavioral profiles of children with NF-1 referred for evaluation of LD would be diagnostic of compromise of anterior brain systems, whereas those of age-, sex-, and IQ-matched LD controls would be heterogeneous.

Neurobehavioral Profiles Associated With Compromise of Anterior Brain Systems

Impairment of anterior brain systems has been associated with both cognitive and behavioral abnormalities. Cognitive deficits can include preserved overlearned skills in the face of diminished performance when a task requires speed or mental tracking, lack of familiarity and structure, or perceptual or response complexity [Lezak, 1983]. Adults with such deficits can be easily overwhelmed when confronted with complexity and display a limited repertoire of responses. This rigidity can be manifest in social behavior as well, resulting in difficulty with conversational turn-taking, poor appreciation of different perspectives, and impaired social judgment [Mesulam, 1985]. The frontal syndromes of childhood have been similarly described, with diminished cognitive and social flexibility [Gratton and Eslinger, 1991; Dennis, 1991]. Executive functions and behavioral regulation are also typically affected in both adults and children.

Such syndromes can be seen not only in individuals with damage to the frontal lobes, but also in those with damage to subcortical structures that function as a primary relay station to the frontal cortex [Lezak, 1983; Gratton and Eslinger, 1991; Cummings 1984; Mendez et al., 1989]. Hence, in the present study, the diagnostic term "frontal" refers to a functional network comprising anterior structures at the cortical and subcortical levels. We predicted that the neurobehavioral profiles of children with NF-1 would be marked by a characteristic behavioral profile involving most prominently poor behavioral regulation, inefficient executive control (cognitive flexibility), and deficient social discourse [Dennis, 1991].

Neurobehavioral outcomes were conceptualized using the systemic approach to neuropsychological assessment [Bernstein and Waber, 1992]. This method integrates information from multiple sources, including history, behavioral observations, and test scores, to generate a neuropsychological diagnostic formulations.

The present study was based on a retrospective review of information entered into a clinic database at the time of evaluation. Children with NF-1 were identified and matched for sex, age, and IQ to children without known genetic disorders referred to the same clinic. The database includes neurological findings, behavioral observations, test performance, and functional and neurobehavioral diagnostic formulations.

To test the central hypothesis, a priori predictions were made regarding the diagnostic profile formulated by the examining clinician as well as specific items from the neuropsychological evaluations, all of which were recorded in a database at the time the child was seen. It was predicted that items from the neuropsychological evaluation designated on an a priori basis to be consistent with a frontal profile (target behaviors) would be more prevalent in the NF/LD group than in the LD group, whereas those behaviors not included in the frontal diagnostic cluster would be equally prevalent in both groups. Neurological examinations were compared between groups to further delineate biological substrates for neurobehavioral profiles.

MATERIALS AND METHODS

Subjects

Ten children with NF-1 were identified from the records of the Learning Disabilities Program at the Children's Hospital, Boston (1986–1992). All children referred to the program for evaluation who carried a diagnosis of NF-1 were ascertained. NF-1 had been diagnosed by the neurofibromatosis clinic neurologist (B.R.K.) using standard criteria. Table I shows age, estimated IQ, sex, and inheritance pattern for these patients. LD control cases were chosen from the same clinic database, the only exclusionary criterion being documented genetic disease. Matching criteria were age, sex, and estimated IQ. IQ scores were derived on the basis of the Vocabulary and Block Design Subtests of the Wechsler Intelligence Scale for Children-Revised [WISC-R; Telligen and Briggs, 1967]. The same-sex LD

TABLE I. Characteristics of NF-1 Patients

Subject	Age	Sex	IQ (estimated)	Familial (F)/ Sporadic (S)
1	9–4	F	90	S
2	8–8	F	80	S
3	8–0	F	88	S
4	7–2	F	89	F
5	8–5	F	97	S
6	11–0	F	103	F
7	6–5	M	80	S
8	11–7	M	83	UNK
9	11–9	M	68	S
10	9–4	M	68	F

child whose chronological age and derived IQ most closely matched that of the proband was chosen.

Overview of Method

The neurological examination and neuropsychological assessment were reviewed and compared between the NF/LD and LD groups. Since the study was retrospective, examining neurologists and neuropsychologists were necessarily aware of the diagnosis of NF-1. They were not, however, aware of the study hypothesis.

Neurological Evaluation

Each child's medical history was recorded in a structured interview with the parent. A neurological examination was performed with an emphasis on extended features.

History. Variables from the neurological history that were examined included a) developmental milestones (language and motor); b) family history of learning disorders; and c) family history of non-right handedness.

Examination. The standard classic and extended pediatric neurological examinations were performed. The classic examination assessed mental state, including rating of quality of attention and motor coordination, cranial nerves, the motor system (tone, bulk, and strength), reflexes, the sensory system, and gait. The extended examination included tests of praxis (Berges-Lezine Praxis Battery), graphesthesia, stereognosis, motor sequencing (Luria Fist-Edge-Palm), and timed motor performance [Denckla, 1973, 1974].

Neuropsychological Assessments

The neuropsychological assessment included 3 components: behavioral observations, neuropsychological tests, and diagnostic formulation (functional and neuropsychological).

Behavioral observations. Spontaneous behavior relevant to the neuropsychological diagnostic formulation was documented by a checklist of behavioral observations entered by the neuropsychologist at the time of evaluation. Categories included 1) social and affective status; 2) language and speech; 3) attention; and 4) motor.

Tests. Neuropsychological tests included 1) selected subtests from the WISC-R (Information, Vocabulary, Digit Span, Block Design, and Picture Arrangement); 2) the Rey-Osterrieth Complex Figure, (ROCF; copy, immediate, delay). This set was not the entire clinical test battery, but those tests for which data were complete.

Formulation. Ratings of psychological function based on behavioral observation and test performance were assigned in a binary fashion for the following categories: language, memory, motor, attention, visuomotor, social/affective. The neuropsychological diagnostic formulation was framed in terms of the 3 neural axes (anterior/posterior; left/right; cortical/subcortical).

Data Reduction

Neurological abnormalities (Table II) were scored as present or absent and then rank ordered by frequency within each group to determine relative prevalence. Based on current literature on NF [Rubenstein and Korf, 1990], 2 anthropometric measures, head circumference and height, were predicted to be affected as well.

TABLE II. Neurological Examination Items

1. Attention	19. Stressed gait
2. Praxis	20. Balance
3. Visual fields	21. Hopping
4. Extra ocular movement	22. Timed motor
5. Pursuit	23. Alternating hand postures
6. Optokinetic nystagmus	24. Fist edge palm
7. Other cranial nerves	
8. Deep tendon reflexes	
9. Babinski	
10. Muscle bulk	
11. Muscle tone	
12. Strength	
13. Choreiform movements	
14. Primary sensory	
15. Corticosensory	
16. Romberg	
17. Cerebellar testing: finger to nose	
18. Gait	

Neuropsychological findings were evaluated in terms of 1) behavioral observation/functional ratings; 2) neuropsychological diagnostic formulation; and 3) test scores. The behavioral observation and functional ratings were grouped together as a composite behavior score. Each item was designated a priori as being a member of either the "F" or frontal (18 items) or "Non-F" or nonfrontal (20 items) cluster (Table III). Numbers of items scored as present were tallied for each cluster to generate 2 summary scores for each child. The frontal cluster are those items that reflect self-regulation, cognitive flexibility, vulnerability to interference, and activation of social knowledge.

Finally, the distribution of neuropsychological diagnoses as recorded at the time of evaluation was compared for the 2 groups.

RESULTS

Neurological Evaluation

History. A history of delayed language and motor milestones was more prevalent in the NF/LD than the LD group (Table IV). The prevalence of familial LDs and non-right handedness was comparable, however.

Examination. A 2-way, Group X Sex analysis of variance (ANOVA) revealed that neurological abnormalities were more prevalent in the NF/LD group, $F(1, 16) = 16.50$, $P < 0.0009$. Specific abnormalities, rank ordered by frequency in each group, are presented in Table V.

In addition, as expected, megencephaly ($P = .027$) and short stature ($P = .016$) were more prevalent in the

TABLE III. F and Non-F Clusters From Neuropsychological Assessment*

F cluster (18)	Non-F cluster (20)
1. Immature or socially unaware in social interactions (B)	1. Self-esteem: low or oppositional (B)
2. Disinhibited language (B)	2. Cooperation with testing (B)
3. Poor formulation of discourse (B)	3. Sound structure (B)
4. Disorganized language comprehension (B)	4. Speech (B)
5. Excessive digressiveness and/or attractability to stimuli (B)	5. Voice (B)
6. Behavioral, verbal, or motor disinhibition (B)	6. Fine motor: tic/tremor (B)
7. Concrete style (F)	7. Hand use (B)
8. Stimulus-bound style (F)	8. Drawing hand (B)
9. Difficulty with complexity (F)	9. Pencil grip R (B)
10. Difficulty with precision (F)	10. Pencil grip L (B)
11. Lack of persistence (F)	11. Posturing with writing (B)
12. Graphomotor problem (F)	12. Language overall (F)
13. Motor skills problem (F)	13. Language input (F)
14. Motor activity level problem (F)	14. Language output (F)
15. Concentration (F)	15. Visual rotations (F)
16. Vigilance (F)	16. Constructional apraxia (F)
17. Affect (F)	17. Visual memory (F)
18. Social (F)	18. Verbal memory (F)
	19. Preoccupied (F)
	20. Episodic lapses of attention (F)

* B, behavioral observation; F, functional review of systems.

NF/LD group. There was, however, an unanticipated sex difference: All 6 NF/LD females exhibited megencephaly, but none of the males.

Neuropsychological Evaluation

Behavior. Behavior scores were analyzed by a 2(Sex) × 2(Group) × 2(Type) repeated-measures ANOVA, with Type (F or Non-F) the repeated measure. There was a 2-way, Group × Type, interaction, $F(1, 16) = 4.5$, $P = .05$. As predicted, group differences emerged for the F behavioral cluster only. This effect was modified, however, by a marginally significant 3-way, Sex × Group × Type, interaction, $F(1, 16) = 3.9$, $P = .06$. NF/LD females achieved higher scores on the F behavioral cluster than did NF/LD males or LD controls (Table VI). By contrast, there were no effects of Group or Sex for nontarget behaviors.

Test performance. WISC-R scores were compared by t-test (Table VII). Although mean estimated IQ scores do not differ, Vocabulary and Information subtest scores are lower for the NF/LD group than the LD group.

Organization and Style scores for the ROCF were analyzed by a 2(Group) × 3(Condition) mixed-effects ANOVA. The LD group drew better organized designs, $F(1, 15) = 6.84$, $P < .02$, and produced the figure in a more configurational fashion, $F(1, 14) = 7.36$, $P < .02$. There was no effect of Condition, indicating that the between-subjects effects were comparable for copy and recall conditions.

Neuropsychological diagnostic formulation. The examining clinician assigned a frontal/subcortical (F/SC) diagnosis for 6 of the 10 NF/LD patients but only 2 LD patients. Once again, however, sex was a relevant factor. Five of 6 NF/LD females were assigned a F/SC diagnosis, but only one of 4 males (Table VIII).

COMMENTS

As predicted, a neurobehavioral profile observed in NF-1 children referred for LD was consistent with compromise of functions associated with anterior brain systems. Structured evaluation of behavioral observations revealed a consistent profile in the NF/LD group, characterized by verbal and motor disinhibition, compromised social discourse, poorly regulated attention, and awkward motor output. Not only was the clinical neuropsychological diagnosis of F/SC overrepresented in

TABLE IV. Neurological History

	NF/LD (N = 10)	LD (N = 10)	Fisher exact probability
Delayed motor milestones	6	1	0.0271*
Delayed language milestones	6	1	0.0271*
Family history of LD	6	5	0.3150
Family history left handedness	7	6	0.3251

* Significant.

TABLE V. Number of Individuals Exhibiting Specific Neurological Abnormalities by Group

NF/LD (N = 10)		LD (N = 10)	
Balance	8	Stressed gaits	4
Stressed gaits	7	Corticosensory	4
Hopping	7	Optokinetic nystagmus	2
Pursuit	6	Pursuit	2
Attention	6	Balance	2
Timed motor examination	6	Timed motor examination	2
Luria fist edge palm	6	Alternating hand posture	2
Alternating hand postures	4	Luria fist edge palm	2
Optokinetic nystagmus	3		
Other cranial nerve	3		
Deep tendon reflex	2		
Corticosensory	2		

the NF-1 group, but specific diagnostically relevant behaviors were more frequent as well.

Surprisingly, this highly consistent finding was documented only for girls. Both the F/SC neuropsychological diagnostic formulation and megencephaly were consistently observed in the females but not in the males. Given the autosomal dominant inheritance patterns of NF-1, such a consistent sex difference in behavioral characteristics was unanticipated.

The neurological examination, which revealed more abnormalities in the NF-1 group, was consistent with compromise of anterior/subcortical systems, although no sex differences were detected. The difficulties documented involving equilibrium, synkinetic movements, hopping, and timed motor coordination implicate motor output systems. Taken together with the increased prevalence of deficits in attention, pursuit, and optokinetic nystagmus, the findings are consistent with specific dysfunction affecting frontal systems. Although some of the same items were abnormal in the LD group, they were far less frequently so.

MRI findings reported by other investigators are consistent. Studies of children with NF-1 indicate that the number of locations of abnormal T_2 high-intensity signals correlates with the degree of depression of Full Scale IQ relative to that of nonaffected sibs [Hofman et al., 1994]. Many of these signals are found in basal ganglia and subcortical white matter, which are thought to play a significant role in motor coordination and integration of complex cognitive functions. North et al. [1994] posited that compromise of subcortical neural pathways results in decreased cognitive abilities in NF-1.

There was clearly a downward shift in the general cognitive ability levels of this referred population, with an average estimated IQ level of 80. Even though the 2 groups were matched for IQ, the NF/LD group tended to score more poorly on the Verbal subtests of the WISC-R and performance on the ROCF, which can be sensitive to impairment of frontal systems [Lhermitte et al., 1972; Waber and Bernstein, 1995], was clearly more disordered. Dyspraxia, as documented in the neurological examination, can also be contributory to poor constructural abilities, however.

To summarize, girls with NF-1 referred for evaluation of LDs demonstrated a distinctive neurobehavioral profile that was not IQ specific, as well as a high rate of megencephaly. This profile reflects spontaneous behavior observed in the context of clinical assessment to a far greater extent than cognitive test scores. Such a profile, which may have broader implications for a child's adaptation than isolated deficits in specific cognitive skills, has not been previously described and may be linked to the expression of the genetic abnormality in NF-1.

The conclusions of this study, however, are obviously limited by the retrospective design based on a relatively small series of referred patients. The fact that the behavioral ratings and diagnostic formulations were performed by the same rater is another potential source of bias. Also, the male IQ range (68–83) is lower than the females (80–103), which may also introduce bias as to the sex differences found.

Nevertheless, the observation of an association among female sex, megencephaly, and a characteristic neurobehavioral profile in NF-1 is novel, suggesting

TABLE VI. Mean F and Non-F Behavioral Cluster Scores by Sex and Genetic Diagnosis

Behavioral	F	Non-F
Female (N = 6)		
NF/LD	10.83 (2.78)	7.00 (2.68)
LD	4.66 (3.61)	8.00 (2.00)
Male (N = 4)		
NF/LD	5.24 (5.18)	8.00 (2.16)
LD	4.50 (0.57)	7.50 (2.88)

TABLE VII. Mean Scores for WISC-R Estimated IQ and Individual Subtests

	NF/LD	LD
(Estimated) Full Scale IQ	80.9	82.1
Information	6.5	7.8*
Vocabulary	6.3	7.8*
Digit span	7.5	8.0
Picture arrangement	8.6	8.9
Block design	7.1	6.0

* $P < .1$.

TABLE VIII. Prevalence of Megencephaly and F/SC Neuropsychological Diagnosis by Sex

	F (N = 6)	M (N = 4)
Megencephaly (.98 percentile)		
NF/LD	6	0
LD	2	0
F/SC profile		
NF/LD	5	1
LD	1	1

that some children with NF-1 are at greater risk for neurobehavioral difficulties than others. A larger, prospectively ascertained sample currently is being evaluated to determine whether the associations observed here are indeed representative of the larger population of NF children.

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